UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/069,847	04/30/98	HAN M	010091-035

HM12/1130

ROBIN L. TESKIN
BURNS, DOANE, SWECKER & MATHIS
P.O. BOX 1404
ALEXANDRIA VA 22313-1404

EXAMINER	
FREDMAN, J	
ART UNIT	**PAPER NUMBER**
1655	15

DATE MAILED: 11/30/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/069,847	Han et al
Examiner	**Group Art Unit**
Jeffrey Fredman	1655

☒ Responsive to communication(s) filed on *October 27, 1999 and November 8, 1999*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *64-101* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *64 and 65* is/are allowed.

☒ Claim(s) *66-100* is/are rejected.

☒ Claim(s) *101* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. The rejection of claims 15, 16, 18-20, 32, 35, 56, 57 and 62 under 35 U.S.C. 102(b) as being anticipated by Takahashi is withdrawn in view of the amendment.

3. Claims 66-68, 70, 77, 81, 84, 85, 87, 88, 90-92, 94, 97 and 99 are rejected under 35 U.S.C. 102(e) as being anticipated by claims 1-13 of Livak et al (U.S. Patent 5,538,848).

Livak teaches a method for monitoring nucleic acid amplification comprising: performing nucleic acid amplification on a target polynucleotide using a nucleic acid polymerase having 5'-3' nuclease activity, a primer capable of hybridizing to said target polynucleotide, and an oligonucleotide probe capable of hybridizing to said target polynucleotide, 3' relative to said primer, said oligonucleotide probe having a fluorescent reporter molecule and a quencher molecule capable of quenching the fluorescence of said reporter molecule, said oligonucleotide probe existing in at least one single-stranded conformation when unhybridized where said quencher molecule quenches the fluorescence of said reporter molecule, said oligonucleotide

probe existing in at least one conformation when hybridized to said target polynucleotide where the fluorescence of said reporter molecule is unquenched, the fluorescence intensity of said reporter molecule being greater than the fluorescence intensity of said quencher molecule when said probe is hybridized to said target; polynucleotide, said nucleic acid polymerase digesting said oligonucleotide probe during amplification to separate said reporter molecule from said quencher molecule; and monitoring the fluorescence of said reporter molecule, the generation of fluorescence corresponding to the occurrence of nucleic acid amplification (column 13, claim 1) Livak further teaches the method wherein said nucleic acid polymerase is a thermostable nucleic acid polymerase (column 13, claim 2). Livak further teaches the method wherein said reporter molecule is a fluorescein dye and said quencher molecule is a rhodemine dye (column 13, claim 3). Livak further teaches the method wherein said reporter molecule is separated from said quencher molecule by at least about 15 nucleotides (column 13, claim 4). Livak further teaches the method wherein said reporter molecule is separated from said quencher molecule by between about 15 and 60 nucleotides (column 13, claim 5). Livak further teaches the method wherein said reporter molecule is separated from said quencher molecule by at least about 18 nucleotide (column 14, claim 6). Livak further teaches the method wherein said reporter molecule is separated from said quencher molecule by between about 18 and 30 nucleotides (column 14, claim 7). Livak further teaches the method wherein the reporter molecule is attached to either a 3' or 5' terminal nucleotide of the probe (column 14, claims 8 and 10). Livak further teaches the

wherein the quencher molecule is attached to either a 3' or 5' terminal nucleotide of the probe (column 14, claims 9 and 11).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 66-68, 70, 73, 75, 77-92, 94, 97 and 99 are rejected under 35 U.S.C. 103 as being obvious over Livak et al (U.S. Patent 5,538,848).

Claims 1-13 of Livak et al (U.S. Patent 5,538,848) teach the limitations of claims 66-68, 70, 77, 81, 84, 85, 87, 88, 90-92, 94, 97 and 99 as discussed above.

Claims 1-13 of Livak et al (U.S. Patent 5,538,848) do not teach the measurement method, the linkers or the use of different nucleic acid types.

Livak teaches a method of continuously detecting a specific nucleic acid sequence within a nucleic acid amplification reaction comprising the steps: a) obtaining a fluorescently labeled modified DNA oligonucleotide (and expressly teaching the use of RNA (column 4, line32) labeled at both ends of the oligonucleotide with a fluorescence acceptor and fluorescence donor which include fluorescein and rhodamine (column 3, lines 29-47) where the fluorophores are attached by 12 carbon linkers (column 6, lines 40-62) and spaced about seven basepairs apart (column 2, lines 45-57), b) contacting the oligonucleotide with an enzyme that facilitates nucleic acid cleavage (column 3, lines 43-47), c) continuously detecting the cleavage by detection of a change in fluorescence intensity as the cleavage occurs (column 1, lines 44-51). Livak expressly teaches the use of a microplate reader which reads by an analog measurment of energy transfer(column 8, lines 10-28).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the claimed method of Livak with the elements taught by Livak since Livak states "In view of the above, the application of techniques for real-time monitoring of nucleic acid amplification would be facilitated by the availability of conveniently synthesized probe having efficient hybridization characteristics and distinct fluorescent characteristic in a bound double stranded state and an unbound single stranded state (column 2, line 66 to column 3, line 4)".

6. Claims 66-70, 73, 75, 77-94, 97 and 99 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Livak in view of Walder et al (WO 89/09284).

Claims 1-13 of Livak et al (U.S. Patent 5,538,848) in view of Livak teach the limitations of claims 66-68, 70, 73, 75, 77-92, 94, 97 and 99 as discussed above. Claims 1-13 of Livak et al (U.S. Patent 5,538,848) in view of Livak do not teach catalytic hybridization amplification.

Walder teach the method of catalytic hybridization amplification (figure 3, 4A and 4B).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescence detection method of Livak with the catalytic hybridization amplification method of Walder since Walder states "This results in a large increase in the level of sensitivity of the method compared to current diagnostic tests, all of which are based on stoichiometric hybridization reaction in which the target sequence is able to bind one, and only one, molecule of the probe (page 42, paragraph 2)". An ordinary practitioner would have been motivated to combine the method of Livak with the method of Walder for the expected benefit of increased sensitivity.

7. Claims 66-68, 70, 71,73, 75, 77-92, 94, 95, 97 and 99 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Livak in view of Backman (EP 439 182 A2).

Claims 1-13 of Livak et al (U.S. Patent 5,538,848) in view of Livak teach the limitations of claims 66-68, 70, 73, 75, 77-92, 94, 97 and 99 as discussed above. Claims 1-13 of Livak et al (U.S. Patent 5,538,848) in view of Livak do not teach ligase chain reaction.

Backman teach the method of Ligase chain reaction (Page 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescence detection method of Livak with the ligase

chain reaction method of Backman since Backman states "One of the great strengths of amplification reactions is their ability to detect exceedingly small numbers of target molecules (page 2, lines 36-37)". An ordinary practitioner would have been motivated to combine the method of Livak with the method of Backman for the expected benefit of increased sensitivity.

8. Claims 66-68, 70, 72-92, and 96-100 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Livak in view of Conrad (U.S. Patent 5,652,099).

Claims 1-13 of Livak et al (U.S. Patent 5,538,848) in view of Livak teach the limitations of claims 66-68, 70, 73, 75, 77-92, 94, 97 and 99 as discussed above.

Conrad teaches methods of single photon counting and time resolved fluorescence as well as measurement of the fluorescent lifetimes (Column 33, example 9).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescence detection method of Livak with the detection methods of Conrad since Conrad states the assay provides "a broad basis for the design of diagnostic detectors for a wide variety of nucleic acid assays and diagnostics. It is an important consequence of the invention that sensitivity and signal to noise ratios are a function of the number of photons counted and the number of time periods over which counting is done (column 34, lines 14-19)".

Allowable Subject Matter

9. Claims 64 and 65 are allowed.

The cited prior art does not teach or suggest detection of ligation by a continuous fluorescent assay.

10. Claim 101 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. As discussed in the interview, where the linker is 12 carbons or greater, there is the unexpected result that linker inhibits quenching due to this length. This claim is therefore novel and unobvious due to the cited result. The broader claims, which use functional language, read on the use of any linker broadly, since any linker, including those used by Livak, will necessarily inhibit quenching, to a greater or lesser degree. The examiner agrees that the evidence presented shows that 12 carbons represents essentially complete inhibition.

Response to Arguments

12. Applicant's arguments filed October 27, 1999 have been fully considered but they are not persuasive.

Applicant's arguments are successful in removing all of the references except for the Livak patent and rejections which depend upon the Livak patent. Applicant submitted a 1.131 declaration to overcome the 102(e) rejection over Livak. This is not effective in this case because the claims, both as originally filed and the new claims, directly conflict with the claims of the

Livak patent. As MPEP 2306 notes, when claims of an application and patent conflict, "The patent is a reference against the application under 35 U.S.C. 102(e), unless the applicant has filed a showing under 37 CFR 1.608." Since no showing has been made under 37 CFR 1.608(a), the Livak patent remains a valid reference.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Fredman, Ph.D. whose telephone number is (703) 308-6568.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1634

November 24, 1999